

# **Adolescents in HIV Prevention Clinical Trials**

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# Challenges With Adolescent and HIV Disease

# Craig Wilson – Epidemiology

Dynamics of youth epidemic changing

US explosion in AA, MSM since 2000

Much higher prevalence in Sub-Saharan Africa

Consider local epidemiology in designing trials

Highest risk people may not be appropriate for trials

Engage lowest age possible at earliest time

Youth focused interventions



# Bret Rudy – Medicine and Research

Unique biological and psychosocial features at different stages of adolescence

Behavior and biology intertwined – sexual ID

REACH trial – periodic, retention rates to 91%

Unexpected drivers of retention

Understanding ppt needs key to research success

Poverty, homelessness, social support

Researchers / clinicians present barriers



IAVI,  
2006

# Paul Krogstad – Immunology

Age dependent immune responses

0-1 mo – ↓ innate and adaptive

24 mos – ↓ T independent (encapsulated)

End of life deficiencies similar to early  
CD4 inversely proportional to age

Adolescence is beginning of  
immunological senescence

↓ Thymic tissue, early antigens

Vaccine responses decrease with age

Greater T cell responses in young vs. old

Different determinants of immune failure



Abduction of Psyche,  
Bouguereau, ~1900

# Sybil Hosek – Behavioral Considerations

## Cognitive development

Dynamic biological process → intense emotions

## Psychological development

Mood changes, adolescent specific norms

## Social development – Sexuality

## Sexual Risk Behavior – Concurrence / Back-Up

## Youth Risk Behavior Surveillance System

Risky sexual behavior, substance use  
amongst high school students

Consider systems in which we exist



# Gary Lawrence – Youth Perspective

Sex education inadequate, but did talk about HIV

Youth do “anything and everything”

HIV status affects relationships

Safe-Sex – Don’t ask, Don’t tell

Condom use affected by substance use, personal issues, relationship dynamics, exploration

Youth have difficulty with regular meds even if HIV infected



The Master Bedroom, Van Gogh

# Biomedical Prevention Interventions



# Mickey Lally – Biomedical Intervention

Goal of concurrent licensure in youth  
CFR – appropriate risk : benefit balance  
When can we include adolescents?

Scientific and / or regulatory necessity

Risk : benefit balance

Why include adolescents?

Efficiency – Immunogenicity

Practical – licensure

Ethical obligation

HIV Vaccine experiences

Lessons from HPV vaccines



# Glenda Gray – Vaccine Trials

Understanding adolescent epidemiology and culture will facilitate research

Need for adolescent data

Phambili – Merck vx in RSA heterosexuals

About 1/3 participants 18-20 years old

Considerations

Ethical-Legal

HIV knowledge good amongst RSA youth

High willingness to participate

Plans for preparedness study using HPV vaccine



HIV Vaccine Trials  
Network

# Ian McGowan – Microbicides

Efficacy : Safety balance

Window of vulnerability amongst adolescent girls

MTN 004 targeting 18-24 year olds

Telephone diary sub-study

R01 – microbicide safety and acceptability

young MSM, who are difficult to engage

Many challenges to adolescent engagement

Need to enroll younger age groups in research



# Linda-Gail Bekker – PrEP

Pre-exposure dosing increases efficacy

Meds ideally not used in treatment, few side effects, no disinhibition

FTC/TDF (Truvada) potential

- Import of CASI in behavioral interventions

- Decreased risk behavior during PrEP

Adolescents

- Adherence concerns

- Studies suggest similar dosing to adults

- Concerns about toxicity

Next steps: ramp up safety data collection on TDF, explore other ARV options, possibly roll down iPrex age, other hetero PrEP studies with girls 16-17 yo



Oedipus Solves The Puzzle of the Sphinx, Ingres, 1808

# Greg Zimet – Risk Reduction

## Risk Compensation

May occur, but doesn't neutralize intervention effect

## Preventive Misconception

Overestimate probability of treatment AND assume protection

## Microbicide trials

Little evidence of risk compensation

Qualitative and quantitative disconnect

## HIV vaccine trials

Preventive misconception common

Few findings of increased risk taking

## Little data on adolescents

Preventive misconception more likely?

Need tailored multimedia methods to address preventive misconception and avoid risk compensation

Studies should lay groundwork for addressing these issues



# Drug Development Considerations

# Bill Kapogiannis – Drug Development

Much adolescent use is off-label

Few specific data available, adult extrapolation

Pre-marketing population very restricted

Need for drug data in adolescents

Unique biology, psycho-social and behavior issues

Market influences on development

Considerations – Psychosocial issues,  
physiology, reproductive health,  
ethico-legal



# Elizabeth Garner – HPV Vaccine



## Adolescent Gardasil studies

Data in relevant population required for registration

Immunogenicity, now extended to efficacy

Knowledge of epidemiology drove early inclusion

Infeasibility of efficacy demo → immunobridging

Challenges – parents, consent, need for sexual info, testing, procedures, retention, provider concern

Roll-out – early engagement of stakeholders, push for mandate of vaccination, focus on cancer

## Lessons

Early information and education are key

Empowerment of adolescents re their health is critical

Role of industry?



# Skip Nelson – Ethics and Regs

Risk : Benefit assessment can be very complicated

Benefit of one intervention doesn't offset risk of another

Intervention likely exceeds minor increase over minimal risk,  
need data to establish prospect of direct benefit

Concurrent adolescent licensure depends on data needed

Extrapolation algorithm – if disease course and effects of  
interventions are similar, can extrapolate some data

Can't extrapolate dose or efficacy

Adolescents are adults when they have legal right to  
consent to intervention included in the investigation

International data – FDA has no authority over non-US  
IND studies



# HIV Prevention: Covering All The Bases

# J. Ellen & L-G Bekker – Community

US epidemic focused:

AAMSM>WMSM>AAWSM>WWSM

Community engagement goals: feasibility,  
acceptability, effectiveness



Developing world – RSA has generalized epidemic

Community engagement, CABs have been critical  
WHO/AAVP – include adolescents as soon as  
promising product, must have support for  
adolescent participants

Follow Good Participatory Practice Guidelines

# Kevin Fisher – Advocacy

A truly comprehensive, sustained response must include adolescents

Advocacy objectives: Funding for adolescent research, scientific agenda, political support, community understanding, trial capacity, coordination

Challenges: Money, political and community commitment, adequacy of a good product, advocating for existing and future products, false dichotomies, engaging skeptics

Message: Trials are scientifically, ethically and morally necessary; feasible; and safe

AVAC consultation with bioethicists – Are we engaging the right adolescents?



# Becky Sheets – Ethical, Legal, Social

Most effective public health strategy is to introduce vaccine prior to exposure

Bridging is complicated

Drug concept applicability; Immune correlate

When to include adolescents?

Risk : Benefit – potential social harm

Preparedness still needed

Communications must normalize HIV trials

HHS regulations – US, host, manufacturing countries

NIH requirement to include children, with caveats

To do: Identify cohorts, feasibility, community education, social impact, engage experts, establish friendly sites

